SELF ASSESSMENT ANSWERS

Generalised oedema, lethargy, personality disturbance, and recurring nightmares in a young girl

Q1: What is the likely diagnosis?

The low serum copper and caeruloplasmin concentrations, in the setting of abnormal liver function, hyponatraemia, and profound clotting disturbance point to a diagnosis of Wilson's disease with hepatic failure. In this case, hepatic involvement predominates despite background lethargy, personality change, and depression. The prominent abdominal veins, fluid retention, and ascites are the clinical manifestations of portal hypertension and decompensated liver disease, with poor synthetic function evidenced by a low serum albumin and greatly increased prothrombin time.

Her shortness of breath was secondary to abdominal distention and diaphragmatic splinting due to ascites. A polyclonal immunoglobulin rise is often seen in Wilson's disease and a raised serum B12, which is stored in the liver, is associated with hepatic necrosis.

Q2: What further investigations would confirm the diagnosis?

Classically, serum caeruloplasmin concentrations are very low in parallel with low serum copper levels. Though serum caeruloplasmin estimation alone is not specific enough to diagnose Wilson's disease, concentrations as low as in this case are unusual for any other diagnosis. Caeruloplasmin synthesis can be modestly reduced in decompensated liver disease of any aetiology or in acute liver failure. Protein losing enteropathy, nephrotic syndrome, and malnutrition will also reduce serum concentrations. Conversely, as its synthesis can be stimulated by oestrogens and it is an acute phase reactant, patients taking oral contraceptives or those with acute inflammatory change within the liver may have normal serum levels. In the series reported by Steindl and colleagues,[1] 12 out of 55 patients with Wilson's disease had a normal caeruloplasmin and no Kayser-Fleischer (KF) rings. Free copper concentrations can be calculated—though high values (>200 μg/l) suggest Wilson's disease, diagnosis based on such calculation lacks specificity and is dependent on the accuracy of copper and caeruloplasmin measurement.

A 24 hour copper estimation is a simple and useful confirmatory test with raised values (>100 μg/24 hours) invariably seen in symptomatic Wilson's disease. Concentrations in this case were greatly raised at 461 μg/24 hours (normal range 0–50). Care needs to be taken to ensure the collection is accurate and has not been contaminated (for example extraneous copper in tap water). Verification of the result by a repeat collection is advisable. Borderline values may be obtained in presymptomatic patients or heterozygotes, such results demand further investigation.

A liver biopsy, in itself, may not be diagnostic but is helpful in determining the extent of hepatic involvement and whether or not there is established cirrhosis. In this case, given the background coagulopathy, a transjugular liver biopsy was performed which confirmed established cirrhosis. Fibrosis and moderate inflammatory change was accompanied by extensive collapse of residual liver between regenerative nodules suggesting recent subacute necrosis. A mild increase in copper associated protein and copper accumulation in the hepatocellular nodules was felt to be consistent with Wilson's disease. Occasionally, despite gross hepatic copper excess, histochemical techniques may fail to demonstrate copper. Determination of hepatic tissue copper concentration by neutron activation analysis or atomic absorption spectrometry may clearly indicate hepatic copper overload. Concentrations greater than 250 μg/g dry weight are accepted as diagnostic of Wilson's disease.

Slit lamp examination to look for KF rings may also be helpful, although these are absent in 15%–50% of patients with an exclusively hepatic presentation.[1] It should also be recognised that though KF rings are generally specific for Wilson's disease in children, this is not the case in older patients, where they may be associated with other types of chronic liver disease (usually with a cholestatic component) and non-hepatic diseases. In this case, because of the liver biopsy findings, copper result, and deteriorating clinical condition no slit lamp examination was performed.

Q3: What treatment options might you consider and how would you manage this young girl?

The two main treatment options are chelation treatment with penicillamine or referral to a liver unit for consideration for orthotopic liver transplant (OLT). Chelation therapy is the treatment of choice in patients with compensated liver disease. A satisfactory response, even in the setting of decompensated cirrhosis, ascites, and coagulopathy has been described, as long as encephalopathy has not developed,[2] though early referral to a liver unit is preferable in the setting of deteriorating liver function as OLT is curative.

The usual starting dose is 250 mg daily increasing over a period of a few weeks to an eventual maintenance dose of 1.5 g daily. Approximately 20% of patients will experience side effects such as fever, rash, leucopenia, thrombocytopenia, and lymphadenopathy. An systemic lupus erythematosus-like syndrome and proteinuria may also occur. Trientine is an alternative chelating agent which may be used in those unable to take penicllamine. Elemental zinc inhibits gastrointestinal copper absorption but its long term effectiveness is unproven.

Success of therapy is judged by clinical improvement. This may be slow and 25% of patients with neurological presentations may